SUBMITTING THE IND: AN OVERVIEW

COUNTER TERRORISM PRODUCTS REGULATED BY CBER: EFFECTIVE STRATEGIES TO ASSIST IN PRODUCT DEVELOPMENT

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Donna Chandler, Ph.D.
CAPT, US Public Health Service
Division of Vaccines & Related Products Applications
OVRR, CBER, FDA

SUBMITTING THE IND:
AN OVERVIEW

- Introduction & regulatory process
- IND content and format:
  original submission
- Maintaining the IND
- Common pitfalls
- CT Issues
- FDA guidance

INTRODUCTION
REGULATORY AUTHORITY

- **Food Drug & Cosmetic Act (21 USC 301-392)**
  - FDAMA, November 12, 1997
- **Public Health Service Act (42 USC 262 Section 351)**
- **Code of Federal Regulations**

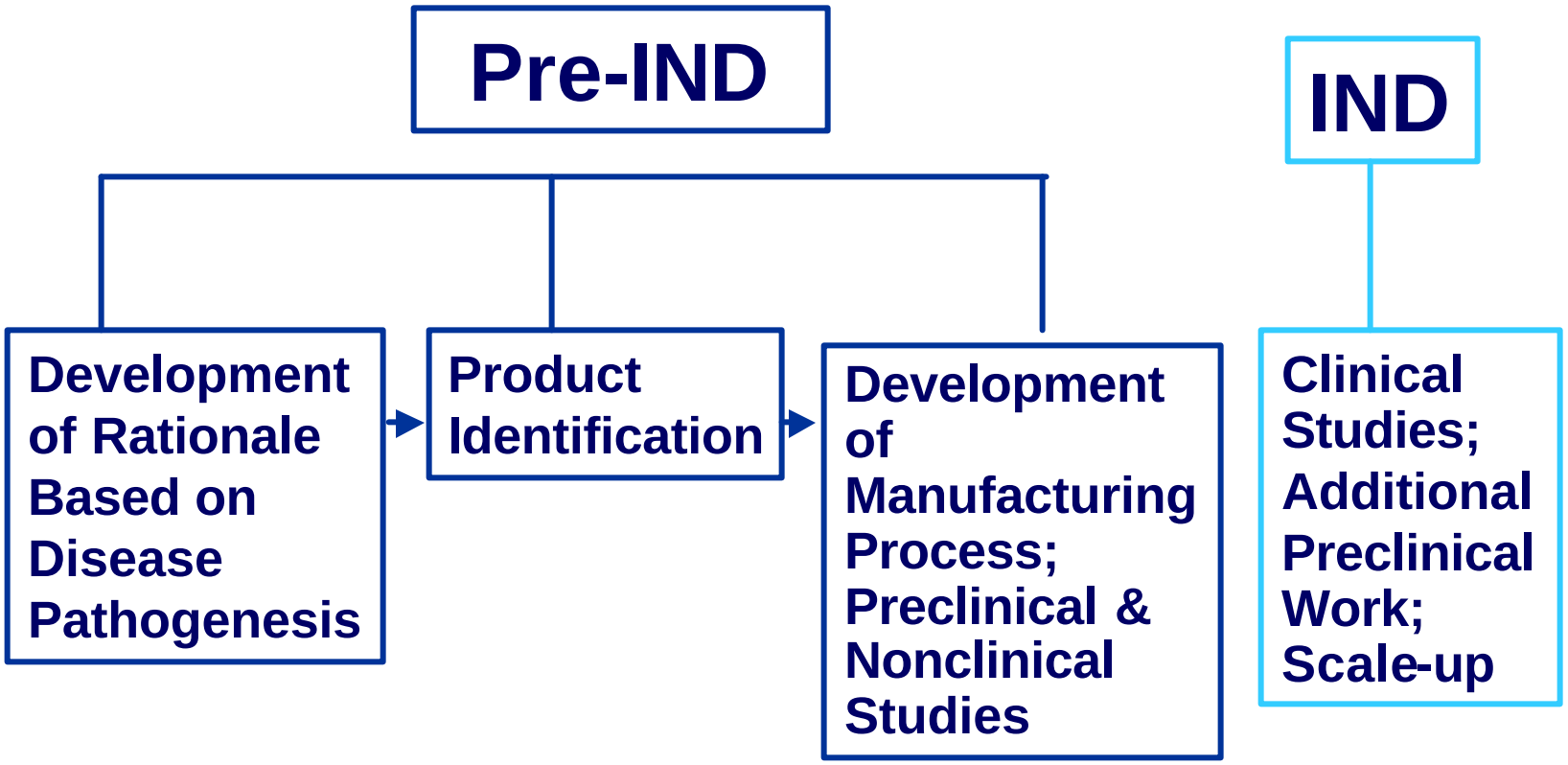
21 CODE OF FEDERAL REGULATIONS (CFR):

Part 600-680	**Biologics**
Part 312	**INDs**
Part 201, 202	**Labeling and Advertising**
Part 210, 211	**cGMPs**
Part 800	***In vitro* Diagnostics**
Part 25	**Environmental Assessments**
Part 50	**Informed Consent**
Part 54	**Financial Disclosure**
Part 56	**Institutional Review Boards**
Part 58	**GLP-Nonclinical Lab Studies**

REGULATORY DEFINITIONS (21 CFR 600.3)

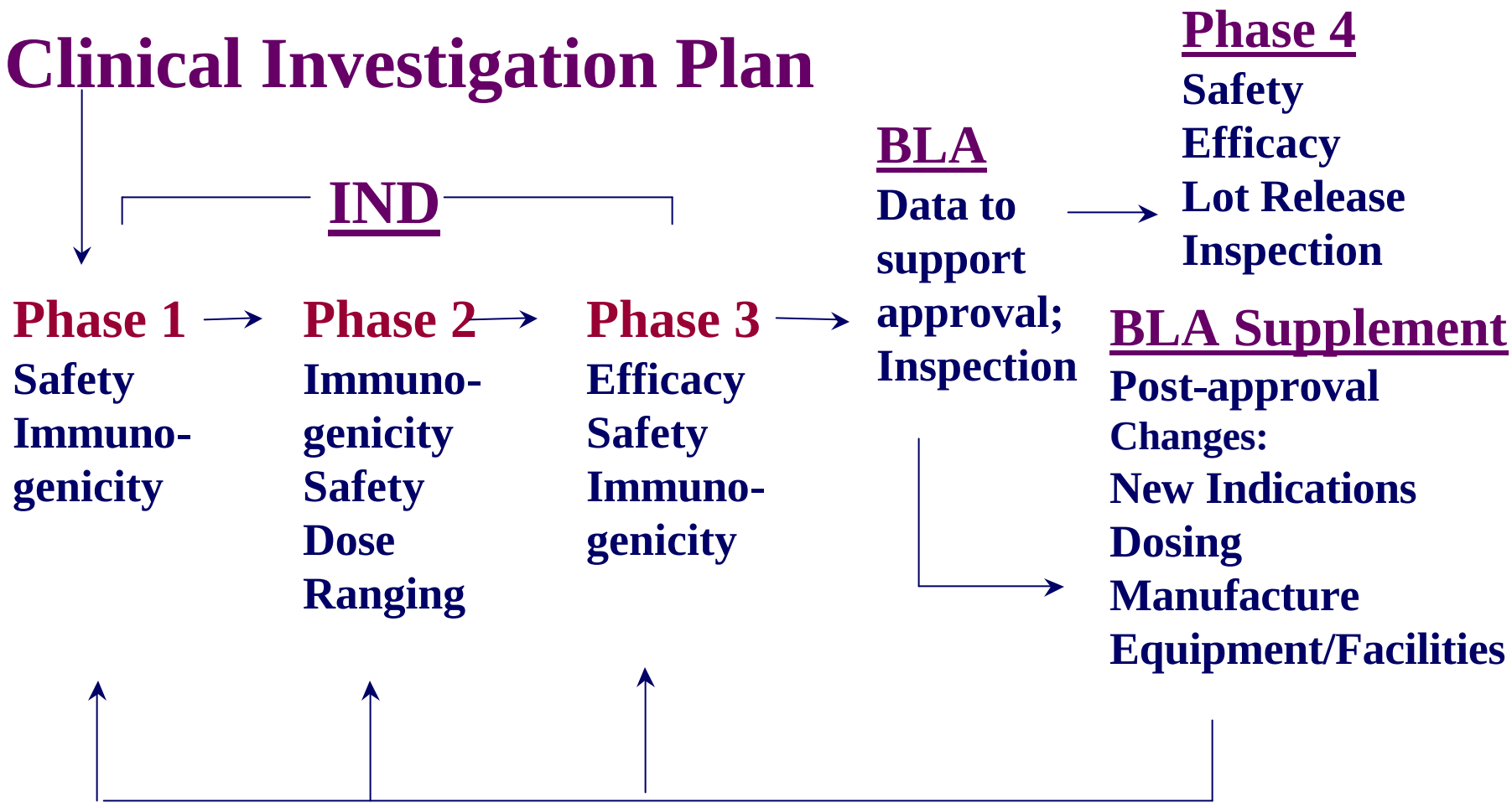
- **Safety**
  - ✓ Relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered...
- **Purity**
  - ✓ Relative freedom from extraneous matter in the finished product...
- **Potency**
  - ✓ Specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

Product Development



IND = Investigational New Drug application

Stages of Vaccine Review and Regulation



IND = Investigational New Drug Application; BLA=Biologics License Application

PRODUCT APPROVAL PROCESS – BIOLOGICS LICENSE APPLICATION (BLA)

- Clinical Safety Data
- Efficacy Data (Clinical, Animal)
- Manufacturing
  - 21 CFR 600 Requirements
  - Process and Quality Control
  - Consistency
  - Lot Release
- Manufacturing Facility(ies)
  - Pre-Approval Inspection
- Product Stability Data – Expiry Dating
- Labeling
- Advisory Committee Discussion

INVESTIGATIONAL NEW DRUG APPLICATION (IND) ROLE IN BIOLOGICS APPROVAL PROCESS

- **Mechanism and process to collect clinical data to support the license application**
  - **Demonstrate safety and efficacy**
  - **Goal: Information for the package insert**
- **Chemistry, manufacturing, and controls (CMC)**
  - **General biological product standards (21 CFR 610)**
  - **Process validation**
- **Assay validation**
  - **Immunogenicity/activity**
  - **Product quality control, lot release**
- **Stability data**

PRE-IND INFORMATION

- **Manufacturing process**
- **Product characterization**
- **Pre-clinical/non-clinical animal toxicity studies for safety**
- **Data to support the IND clinical studies, e.g., dose selection for initial Phase 1 study**
- **Focus: initiate first Phase 1 clinical study**
- **Pre-IND meeting with FDA strongly recommended**

IND GENERAL PRINCIPLES

- **Scope (21 CFR 312.1):**

  "An investigational new drug for which an IND is in effect…is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug."

IND GENERAL PRINCIPLES

"FDA's primary objectives in reviewing an IND are, in all phase of the investigation, to assure the safety and rights of subjects, … FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations…, [21 CFR, 312.22(a)]

IND GENERAL PRINCIPLES

“ …and in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety….”

[21 CFR, 312.22(a)]

IND CONTENT & FORMAT FOR ORIGINAL SUBMISSION (21 CFR 312.23)

- **Cover sheet (Form 1571) *(roadmap)***
- **Table of contents *(what's where)***
- **Introductory statement & general investigational plan *(where you are headed)***
- **Investigator's Brochure *(preliminary package insert)***
- **Clinical Protocol *(plan for collecting safety and activity/efficacy data)***

IND CONTENT & FORMAT (2)
(21 CFR 312.23)

- **Chemistry, manufacturing, and control information *(how you made the product and the testing you did)***
- **Labeling *(investigational use only)***
- **Environmental analysis**
- **Pharmacology & toxicology information *(data to conclude that it is reasonably safe to conduct proposed clinical study)***
- **Previous human experience *(same or similar products)***
- **Additional information *(e.g, critical references)***

CLINICAL PROTOCOL ELEMENTS
21 CFR 312.23 (a)(6)(iii)

- Objectives & Purpose
- Investigator Info (Form 1572, CVs)
- Inclusion/Exclusion/No. of Subjects
- Study Design (e.g., controls and blinding)
- Dose & Schedule
- Monitoring to Meet Objectives
- Monitoring to Minimize Risks

MAINTAINING THE IND

- **Clinical Hold**
- **IND Amendments**
- **Safety Reports**
- **Annual Reports**

CBER CLINICAL HOLD POLICY

- **Regulation: 21 CFR 312.40**
  - ✓ **IND goes into effect (study may proceed) 30 days after FDA receives the IND, unless sponsor is notified otherwise by FDA**
- **Clinical Hold: 21 CFR 312.42**
  - ✓ **Order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation**

CBER CLINICAL HOLD POLICY (2)

- **Grounds - Phase 1:**
  - **Unreasonable & significant risk**
  - **Clinical investigators not qualified**
  - **Inadequate investigator's brochure**
  - **Insufficient information to assess risk**

CBER CLINICAL HOLD POLICY (3)

- **Grounds - Phase 2/3:**
  - **Same Reasons as for Phase 1**
  - **Protocol design inadequate to meet objectives**

CBER CLINICAL HOLD POLICY (4)

- **Notification:**
  - ✓**By telephone or fax**
- **Clinical Hold Letter:**
  - ✓**Within 30 calendar days of hold notification**
- **Additional Comments (Non-Hold) Letter**
- **Review of Complete Hold Response**
  - ✓**Letter within 30 days of receipt of response**

IND AMENDMENTS
(21 CFR 312.30 – 312.33)

- **Protocol Amendments:**
  - ✓**Existing Protocol**
  - ✓**New Protocol**
- **Information Amendments, e.g.,**
  - **Product changes**
  - **Clinical Study Reports**
- **Safety Reports**
- **Annual Reports**

TYPICAL REVIEW TEAM

- Regulatory Reviewer
- Clinical/Medical Officer
- Product Reviewer(s)
- Statistician
- Pharm/Tox Reviewer
- Other, as needed (e.g., cell substrate, assay validation, facilities)

USUAL TIMELINES FOR REVIEW

- **IND: original submission reviewed within 30 days of receipt, study may proceed at 30 days unless placed on clinical hold by FDA**
- **IND amendments:**
  - **New protocols may proceed immediately, although FDA strongly encourages end-of-phase 2 and pre-BLA meetings**
  - **Frequently, discussions occur between FDA and sponsors re: new protocols**
  - **An IND can be placed on hold at any time for safety reasons or for clinical design issues for Phase 2 or 3 studies**
- **Contact regulatory reviewer**

IND SUBMISSIONS: COMMON PITFALLS

- Manufacturing
- Lot Information
- Preclinical Issues
- Protocol Issues
- Administrative
- CT Issues

IND SUBMISSIONS - COMMON PITFALLS: MANUFACTURING

- **Insufficient information**
- **Variable conditions**
- **Lot release test results lacking**
- **Potentially toxic substances - validation of removal or assay for residual component**

Resolution: Provide specific information for proposed clinical lot

IND SUBMISSIONS - COMMON PITFALLS: MANUFACTURING (2)

- **Adventitious agents - inadequate testing or inadequate information on source materials**

IND SUBMISSIONS - COMMON PITFALLS: LOT INFORMATION

- **Lots not clearly identified**
- **Test results not submitted**
- **21 CFR 312.23(a)(7)(i): assure proper identification, quality, purity and strength**
- **21 CFR 610: potency, general safety, sterility, purity, identity**
- **Summary table - stage of manufacture, test, acceptance criteria, test result, data attached**

Resolution: Identify lot number and include QC info for lot to be used in clinical study

IND SUBMISSIONS - COMMON PITFALLS: PRECLINICAL ISSUES

- Pyrogenicity
- Attenuation (live organisms)
- Inactivation/reversion
- Potency (e.g., immunogenicity) data lacking
- GLP safety study (Phase 1), for novel product

IND SUBMISSIONS - COMMON PITFALLS
PRECLINICAL DATA (2)

- **Experimental details lacking**
  - **Need information on lot, dose, route, assays to evaluate immune response**
- **Data lacking to support dose proposed for clinical trial**
- **Pre-IND meeting with FDA not held**

IND SUBMISSIONS - COMMON PITFALLS: PROTOCOL ISSUES

- Include subject diary and case report form(s) to monitor reactogenicity
- Define stopping rules
- Describe assays to evaluate immune response
- Define end point(s) & case definition
- Describe statistical analyses
- Inconsistencies

IND SUBMISSIONS - COMMON PITFALLS: ADMINISTRATIVE

- At least three copies of each original submission and each amendment
- Signed, completed Form 1571 for each submission
- Specific cross-reference:

  IND/MF, date, volume number, page
- Pages numbered sequentially, including attachments
- Clear images of gels and blots

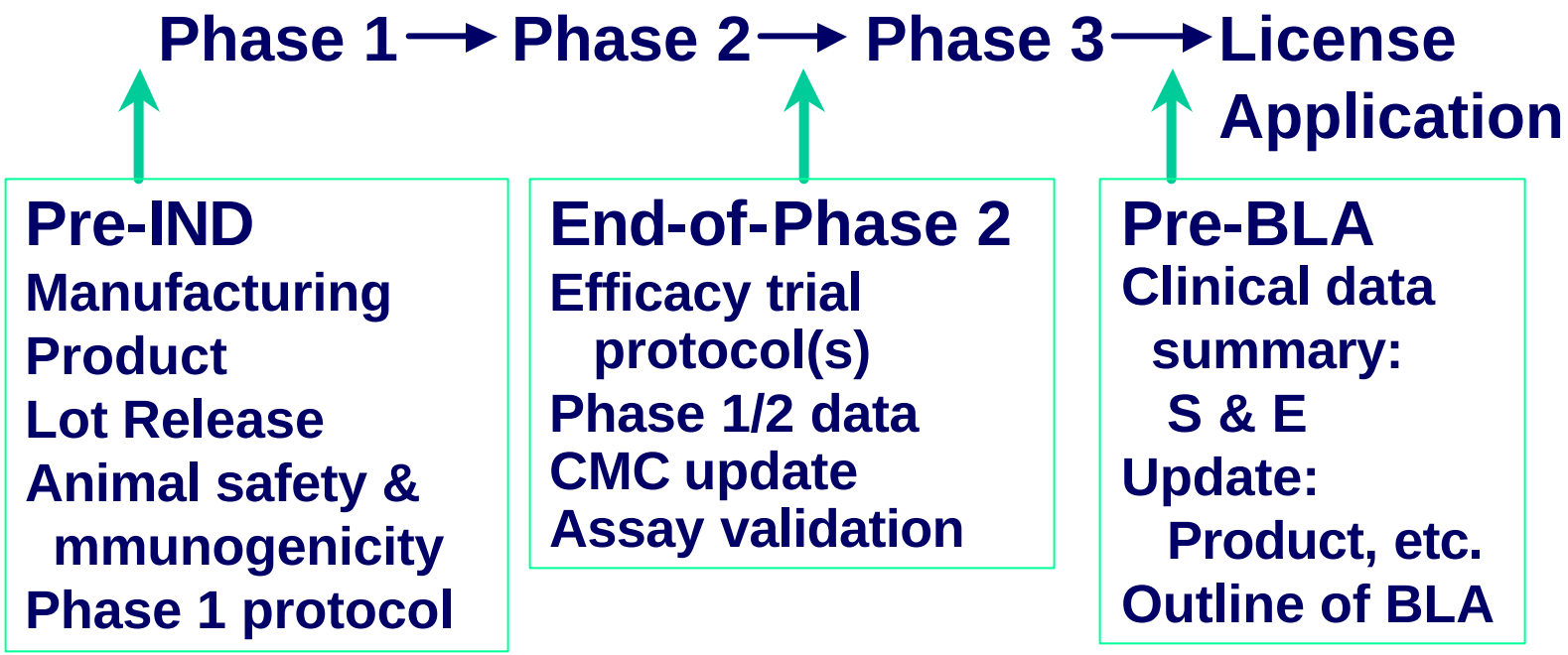
CT- SPECIFIC ISSUES

- **Multiple party involvement**
  - FDA/Sponsor, vs. FDA/Sponsor/Other
  - (Other = DHHS, CDC, NIH, DoD)
- **Expectation for accelerated development**
- **Animal rule vs. clinical efficacy trial**
- **Strategic National Stockpile (prev. NPS)**
- **Use under IND**

GUIDANCE AVAILABLE FROM FDA

- **Meetings**
- **Web page**
- **Telephone/e-mail**

Meetings with FDA
(21 CFR 312.47)



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BLA = Biologics License Application

AVAILABLE CBER GUIDANCE

- Code of Federal Regulations
- Guidance for Industry/Reviewers
- Guidelines
- Points to Consider
- CBER SOPPs
- Federal Register (FR) Notices
- International Conference on Harmonisation (ICH) Documents (U.S., E.U. and Japan)

Guidance Documents - Examples

- **FDA Guidance for Industry**
  - Content and Format of Chemistry, Manufacturing Controls Information and Establishment Description Information for a Vaccine or Related Product (1999)
- **ICH Guidance Documents**
  - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (1998)
  - Quality of Biological Products: Derivation and Characterization of Cell Substrates (1998)

CONTACT INFORMATION

- **FDA documents /Federal Register (FR) notices /FDA regulations**
  - **http://www.fda.gov/cber/publications.htm**
  - **1-800-835-4709 or 301-827-1800**
- **Questions:**
  - **OCTMA@CBER.FDA.GOV (Consumer Questions)**
  - **MATT@CBER.FDA.GOV (Manufacturers Assistance)**
  - **DVRPA: 301-827-3070**

SELECTED REFERENCES

- Baylor N, Midthun K: Regulation & Testing of Vaccines. Vaccines 4th ed, 2004, WB Saunders
- Goldenthal KL, et al: Safety Evaluation of Vaccine Adjuvants. AIDS Res Human Retroviruses 1993; 9:S47-S51
- Chandler D, McVittie L, Novak J:

  IND Submissions for Vaccines. Vaccines: From Concept to Clinic 1999, CRC Press

SUMMARY: IND OVERVIEW

- **IND process: Collect data to support approval (clinical safety and efficacy)**
- **Be specific: Lots to be used, manufacturing process, testing results, procedures for monitoring trial, etc.**
- **Helpful information available on web**
- **Consult FDA (meetings, teleconferences, questions)**